REMARKS/ARGUMENT

RELATED LITIGATION

The original patent, U.S. Patent 6,440,392, (hereinafter " '392 patent"), of which the present application is a reissue application, has become involved in litigation, specifically in a civil action for patent infringement filed in the United States District Court for the Southern District of New York. The civil action is identified as:

> *Unigene Laboratories, Inc. and Upsher-Smith Laboratories, Inc. vs. Apotex, Inc.* and Apotex, Corp, Civil Action No. 06 - cv - 5571 - RPP - THK (S.D.N.Y.).

An Information Disclosure Statement including further details is submitted herewith.

SUMMARY OF THE PRESENT AMENDMENTS

In accordance with Rule 173(g), all of the foregoing amendments are relative to the issued patent -- not relative to the claim language that existed prior to the present amendment. In the present amendment, the concentration range of the bioavailability enhancing agent stated in claim 15 has been narrowed to the same range stated in claim 13.

RESPONSE TO ISSUES RAISED IN THE EXAMINER'S OFFICE ACTION

The Examiner is thanked for her detailed Office Action clarifying the remaining issues to be resolved.

NEW MATTER REJECTIONS

The Examiner rejected claims 13, 41 and 42 under 35 U.S.C. § 112, first paragraph as allegedly setting forth "new matter" by reciting the range of "10-25 mM" for the bioavailability enhancing agent (e.g., citric acid). This ground of rejection is respectfully traversed because the claimed 10-25 mM range is supported by Table 1 at column 5, lines 25-35 of Applicant's '392 patent (corresponding to page 14 of U.S. Patent Application Serial No. 09/776,537 filed February 2, 2001, the application that matured into the '392 patent (hereinafter "'537 application"). Specifically, Table 1 shows that the desired bioavailability response is achieved at both end points of the claimed range -- 10 mM and 25 mM. Good bioavailability is shown at a 10 mM concentration

in Table 1, row 2. Good bioavailability is shown at the other end point of the claimed range, 25 mM, at Table 1, row 3. Applicant, having established effectiveness at both end points of the claimed range has provided the proper basis for claiming the range. There is no *in haec verba* requirement. Newly added claim language may be supported by express, implicit, or even inherent disclosure in the application on its filing date. See MPEP 2163(B).

The Examiner's has also rejected claims 15, 31 and 43-44 on the ground that the stated range of osmotic pressure "from 250 to 350 mOsm/liter is considered new matter. The Examiner states at page 3 of the Office Action that "[t]his range was disclosed in the claims of the parent U.S. Patent 6,044,392, but has no support in the provisional application of 60/180,241." The Examiner is respectfully requested to recheck the records in this regard. After review, and on information and belief, the undersigned believes that the osmotic pressure range from 250 to 350 is supported by claim 15 in <u>each</u> of:

(1) Applicant's '392 patent;

(2) Applicant's '537 application; and

(3) Provisional Application Serial No. 60/180,241 filed February 4, 2000 (to which applicant's 392 patent and '537 application claim priority).

According to applicant's records, claim 15 in the issued patent and in <u>both</u> applications reads as follows:

> "15. A liquid pharmaceutical composition of claim 1 having an osmotic pressure of from about 250 to about 350 mOsm/liter."

Claims (such as above-quoted claim 15) are an integral part of the specification which may be relied upon for enablement under 35 U.S.C. § 112, and to support present claim language without raising "new matter" concerns. MPEP 2163.06. Accordingly, it is urged that the objection to claiming an osmolarity range from 250 to 350 should be withdrawn as fully supported by at least claim 15 of Applicant's specification. It is also pointed out that § 112 only requires support in the application giving rise to the patent (here, the '537 application) - - not in the priority document. Mere lack of support in an earlier priority application merely changes the effective priority date of any claim

unsupported in the priority application, but does not negate enablement in the main application. That said, and as indicated above, the priority application also supports the language at issue.

The Examiner has rejected claims 13-18, 20-21 and 24-44 under 35 U.S.C. § 112, first paragraph, as allegedly setting forth new matter in the recitation of the clause "the aggregate concentration of all such bioavailability . . . ." (Emphasis by the Examiner). This ground of rejection is respectfully traversed . For ease of reference, a more complete text of the language to which the Examiner objected is set forth below.

> ". . . a bioavailability enhancing agent selected from the group consisting of citric acid, citric acid salt and a combination thereof, wherein the aggregate concentration of all such bioavailability enhancing agents is 10-25 mM . . . ."

The above quoted language has three aspects, each of which are properly supported by applicant's application as filed. Those aspects are:

(1) The language requires that (A) citric acid or (B) citric acid salt or (C) a mixture of citric acid and citric acid salt be present;

(2) It identifies the citric acid (or salt or mixture) as "bioavailability enhancing agents" and

(3) It requires that, when a mixture of citric acid and citric acid salt is used, the aggregate concentration of the two -- as opposed to the concentration of citric acid alone or concentration of citric acid salt alone -- must be between 10 and 25 mM.

It is believed that all three aspects are properly supported. Regarding aspect No. 1, the requirement for citric acid and/or salt thereof is fully supported by claim 1 of Applicant's '537 application. It is also supported at page 3, lines 7-8. This corresponds to claim1 and to Col 1, line 52 of Applicant's '392 patent.

Regarding aspect No. 2 , the '537 application also makes clear that the citric acid and/or citric acid salt is a "bioavailability enhancing agent." This function of citric acid and/or citric acid salt is noted, for example, at page 4, lines 11-16, where it is stated that "[t]he present invention also provides a method of improving the bioavailability . . ., which method comprises adding citric acid or a salt thereof . . . ." This corresponds to Col 2, lines 11-17 of the '392 patent. Table 1 (p14 of the

'537 application; Col 5, lines 25-35 of the '392 patent) specifically reports the enhanced bioavailability achieved by various concentrations of citric acid. The results of Table 1 are summarized at page 13, lines 12-15 of the '537 application (Col 5, lines 19-22 of the '392 patent) as follows:

> The results of this study as shown in Table 1 indicate that the bioavailability and peak concentration of rsCT was a function of the concentration of citric acid in the formulation.

Regarding aspect No. 3 of the claim language to which the examiner objected, the original application fully supports that it is the aggregate concentration of citric acid and citric acid salt (where a mixture is used) that must be within the stated concentration range of the claims -- and not merely the separate concentrations of the acid or salt considered individually without reference to the other. This follows naturally from the teachings of the original application that citric acid and citric acid salt may be used interchangeably. It is only the citrate portion of the molecule (or when dissociated, the citrate anion) that citric acid and citric acid salt have in common. It is this common element, therefore, that provides the effects on bioavailability and stability that are reported in Tables 1 and 3 of the '537 application (Col 5, lines 25-35 and Col 6, lines 19-33 of the '392 patent). Note also that in Tables 1 and 3, pH is held constant as the effects of various concentrations of buffered citric acid are measured. This further shows that it is the citrate portion of the molecule (and not the acidic proton of citric acid, for example) that is providing the desired effect. As such, it is the aggregate amount of citric acid and citric acid salt that should be maintained within the concentration ranges set forth in the patent claims whenever a mixture of citric acid and citric acid salt is used. The claim language to that effect that was added in applicant's Amendment of March 2006 (and which was quoted above) was thus fairly based on the '537 application as originally filed and does not constitute a change of the inventive concept that would constitute "new matter". Accordingly, it is urged that the Examiner's rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

THE OBVIOUSNESS REJECTIONS

MPEP 706.02(J) notes that 35 U.S.C. 103 authorizes an obviousness rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office Action:

(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column of page number(s) and line number(s) where appropriate,

(B) the difference or differences in the claim over the applied reference(s),

(C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and

(D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - §2143.03 for decisions pertinent to each of these criteria.

Even if the examiner establishes a *prima facie* case of obviousness, the rejection may be overcome by rebuttal evidence presented by the applicant, for example establishing unexpected results or establishing that the prior art teaches away from the claimed invention. See MPEP 2144.08.

Obviousness rejection over Grebow

Claims 13-14, 17 20-23, 34 and 40-42 stand rejected by the Examiner as allegedly obvious over Grebow et al., U.S. Patent No. 5,026,825. The Examiner alleges that applicant's claimed invention differs from Grebow only by the claimed pH range, and that it would have been obvious to adjust Grebow to applicant's claimed 3.5 - 3.9 pH range based on Grebow's teachings of a pH between 3.0 and 8.0. Applicant respectfully traverses this ground of rejection. Claim 13 is representative of the rejected claims (others are discussed *infra*), and is believed distinguishable from Grebow not only because the broad pH disclosed by Grebow does not fairly suggest the much narrower range of claim 13 (3.5-3.9), but also because Grebow is not believed to suggest, within the meaning of 35 U.S.C. § 103, the claimed concentration of citric acid (and/or citric acid salt) (10-25mM).

Before turning to the relevant text of Grebow, it is useful to summarize certain of Applicant's inventive contributions that are pertinent to the analysis. Among the inventive contributions of Applicant's '392 patent that are neither disclosed nor suggested by Grebow, or the other prior art cited in the Office Action, are the following four items related to the bioavailability enhancing agent:

(1) Citric acid (and/or citric acid salt) enhances the bioavailability of calcitonin administered intranasally, in a concentration-dependent manner. (See, for example, Table 1).

(2) Citric acid (and/or citric acid salt) enhances shelf stability of a nasal calcitonin formulation in a concentration-dependent manner. (See, for example, Table 3).

(3) There exists a concentration range for the citric acid (and/or citric acid salt) which simultaneously permits both good bioavailability and good shelf stability. Absent Applicant's experimental data, the prior art could not have predicted whether such a concentration range even existed. For example, the desired bioavailability response might have required a concentration too high for achieving the desired shelf stability, or vice versa.

(4) Applicant identified the location of critical concentration ranges where the desired bioavailability and shelf stability could be simultaneously achieved. (Tables 1 and 3).

By way of contrast, where the cited prior art addressed citric acid, it was usually in connection with buffering systems for adjusting pH. There is no indication that the cited prior art was utilizing the citrate portion of the molecule for simultaneously achieving good stability and good bioavailability as taught by Applicant. There is no indication that the cited prior art disclosed or suggested any of the above four aspects for using citric acid (and/or citric acid salt), and the prior art's alternative uses tended to lead to far different concentration levels than those recited in applicant's claims. With these distinctions in mind, applicant now addresses specific relevant passages of the Grebow prior art.

Column 11, lines 35-47 of Grebow discusses utilizing a variety of buffer systems to buffer pH in a broad range between 3.0 and 8.0. It is important to remember that pH is a logarithmic scale, and that the range suggested by Grebow is extraordinarily large, the more acidic side of the range being a hydrogen ion concentration 100,000- fold larger than the more alkaline side of the range (10^{-3} on the more acidic side versus 10^{-8} on the more alkaline side). Such a wide variety of potential pH values does not suggest the much narrower range set forth in claim 13 (pH 3.5-3.9) for reasons stated in more detail *infra*.

Grebow does not use citric acid for enhancement of bioavailability and does not teach the narrow 10-25 mM concentration range of claim 13 that Applicant teaches to simultaneously improve bioavailability and shelf stability. Instead, Grebow uses citrate salt/citric acids as one of several alternative buffer systems for achieving the desired 3.0-8.0 pH. For example, Grebow discloses, at column 11, lines 40-43, a number of alternative buffer systems, only one of which is a citrate salt/citric acid buffer. Grebow presents, as equivalent alternatives, phosphate salt/phosphoric acid buffer and acetate salt/ acetic acid buffer. Grebow permits an extremely broad range of buffer concentration from 10-500 mM (stated as 0.01M to 0.5M at column 11, line 44), and states a preference for the range of 50 mM to 200 mM at column 11, line 45 (stated as 0.05 M to 0.2M). This stated preference teaches away from Applicant's claimed 10-25 mM range in a manner that significantly harms results . Table 3 of Applicant's application clearly shows a significant drop in shelf stability beyond 50 mM, and extremely poor shelf stability at 100 mM. See Table 3, row 5 at column 6, line 32 of Applicant's '392 Patent. Yet, Grebow, in direct contradiction to Applicant's teachings, suggests a preference at column 11, lines 44-45 of using a buffer concentration higher than

50 mM and up to 200 mM -- i.e., into a concentration range that extends well beyond any concentration deemed appropriate by Applicant's data.

Grebow's fourteen examples (columns 12-13) are further evidence of Grebow's failure to recognize the importance of utilizing citrate in the narrow concentration range claimed by applicant. Most examples do not use citric acid or citric acid salt at all. Among those that do, far different concentration ranges than the critical ranges identified and claimed by applicant are frequently used. As established by Table 1 attached to the Stern Declaration submitted by Applicant in August 2005, even Grebow examples 7 and 10, which utilized citric acid in the claimed range, did so at a vastly different pH level than recited in claim 13. Indeed, Grebow teaches at column 11, lines 38-39 that any pH is acceptable within an enormous range from 3 to 8 (100,000-fold difference in hydrogen ion concentration from one side of the range to the other).

Thus, in order to arrive at the teachings of applicant's claim 13, it is necessary to (1) selectively choose a citrate buffering system from a wide variety of alternative systems Grebow teaches to be equally useful, (2) ignore Grebow's stated preference for keeping the buffer in a concentration range between 50 and 200 mM and instead use applicant's 10-25 mM range, and (3) specifically adjust pH to applicant's narrow pH range of 3.5-3.9, even though Grebow teaches that any pH between 3.0 and 8.0 would be acceptable. Such parsing and recombining of the prior art represents improper hindsight reconstruction that could not have been suggested from a mere reading of Grebow. To establish a *prima facie* case of obviousness, the teaching or suggestion to make these many combinations must be found in the prior art and not based on applicant's own disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, the broad generic ranges disclosed in Grebow (pH 3-8; buffer 10-500 mM buffer) do not create *prima facie* obviousness for the much narrower claimed ranges of claim 13 (pH 3.5-3.9 and citrate 10-25 mM). As noted in MPEP 2144.05(I), a broad prior art range may fail to render obvious a far narrower sub-range in a manner analogous to other prior art genuses that fail to render obvious a later-claimed specie or sub-genus. See e.g., *In re Baird*, 16 F3d 380 (Fed. Cir. 1994) (specie not obvious over prior art generic formula encompassing specie because, to arrive at the specie, many variables of generic formula had to be selectively chosen in manner not suggested by prior art, and because prior art taught preference for other compounds). Here, as in *Baird*,

applicant's claimed subject matter only arises by manipulation of multiple variables in the broad generic disclosure of Grebow, in a manner not suggested by Grebow, while Grebow instead teaches a preference for a different selection (e.g., 50-200 mM buffer).

Even in the unlikely event that Grebow can be said to present a *prima facie* case of obviousness, that case has been effectively rebutted by (1) evidence that the prior art teaches away from the invention, and (2) evidence that the invention provides unexpected results. First, Grebow teaches away from applicant's claimed 10-25 mM citrate range by stating a preference for 50-200 mM at column 11, line 45. Second, Applicant's Tables 1 and 3 show unexpected results (bioavailability and shelf stability enhancement independent of pH effects) with Applicant's claimed 10-25 mM citrate range. The Grebow prior art used citrate only as a buffer to maintain pH. Applicant's results shown in Tables 1 and 3 are thus different in kind - - not just different in degree - - from the Grebow disclosures.

Thus, claim 13 is distinguishable from Grebow for all the reasons stated above. Additionally, claims 14, 17, 20-21, 34 and 40-42 either recite or incorporate by reference the limitations of claim 13 and are distinguishable for the same reason as claim 13. Claims 22 and 23 recite a broader citrate range, but one that is still sufficiently narrow that the foregoing discussion of Grebow's failure to suggest utilizing that range still applies. Additionally, claims 22 and 23 are method claims wherein the citrate is specifically used for the new purposes that Applicant teaches for the first time in Applicant's Tables 1 and 3. As noted previously, Grebow utilizes its citrate for the purpose of buffering the Grebow formulations. For all of the foregoing reasons it is urged that the rejection for obviousness over Grebow be withdrawn.

Obviousness Rejection Over Kagatani

Claims 13-14, 16-23, 34 and 40-42 stand rejected as allegedly obvious over Kagatani et al. It is assumed that the Examiner intends Kagatani, U.S. Patent 4,788,221, previously of record, although the Office Action recites U.S. Patent 5,026,825 (which is instead the Grebow patent discussed above).

At column 2, lines 25-26 of the Kagatani reference, it is stated that buffers (of which citrate is only one of many possibilities) are utilize to adjust pH to a preferred range between 3 and 5.

However, the concentration of citrate Kagatani uses is far beyond the 10 to 25 mM range required in most of Applicant's rejected claims (and far beyond the 10-50 mM range recited in claims 22 and 23) for enchancing bioavailability and shelf stability. For example, the closest Kagatani examples, Examples 1 and 4, instead utilized a total citrate concentration of approximately 100 mM (comprised of approximately 58 mM citric acid and 42 mM sodium citrate). (See Stern Declaration filed August 2005, Table 1 attached thereto as an addendum). This is an undesirably high concentration that is beyond Applicant's claimed range, and that Table 3 of Applicant's application predicts would have negative consequences for shelf stability. (See especially Table 3, last column, last row).

Among the limitations of claim 13 which are neither disclosed nor suggested by the cited Kagatani reference is the requirement that the bioavailability enhancing agent (whether citric acid, citric acid salt or a mixture of the two) "is 10-25 mM . . . ." The Kagatani concentration is approximately four-fold higher than the top of applicant's claimed range, (two-fold higher than the top of the range stated in claims 22-23), and fails to benefit from applicant's teaching that shelf stability deteriorates at such higher citrate concentrations. See table 3, row 5 at page 16 of the '537 application (column 6 of Applicant's '392 patent). Applicant teaches the undesirability of such high citrate concentrations as used by Kagatani. At column 6, lines 9-15 of Applicant's issued patent (page 16, lines 1-6 of the '537 application), Applicant states that:

> "In the presence of citric acid (10-50 mM) the rate of disappearance of sCT decreased significantly. However, if the concentration of citric acid was further increased, the rate of sCT disappearance from vials stored at 50°C increased in proportion to the amount of buffered citric acid in the formulation."

The foregoing teaching that there is an upper concentration limit for desired calcitonin stability in the presence of citrate is taught by applicant for the first time and is not understood by Kagatani. Kagatani conversely teaches the use of citrate at a very high concentration. This deficiency in Kagatani is not overcome by any contrary disclosures or suggestions to alter Kagatani's citrate concentrations downward into applicant's claimed range.

The foregoing distinction of claim 13 over Kagatani also distinguishes rejected claims 14, 16-21, 34 and 40-42, all of which recite claim 13's citrate range or an even narrower range. Claims 22-23 recited a broader range, but one that is still well below Kagatani's concentration level. These

other claims further distinguish Kagatani by additional limitations. For example and not by way of limitation, claim 16 adds the further limitation of using 0.1% by weight of polyoxyethylene(20) sorbitan monooleate. This can have an important effect on surface tension optimizing droplet size of a spray pharmaceutical, and increasing bioavailability. See for example, Applicant's '392 patent at column 2, lines 56-65. Claim 18 includes the same surfactant limitation and further recites a specific mixture of alcohol compounds. Likewise, claim 19 includes each of (1) a preferred surfactant and surfactant concentration, (2) a preferred specific mixture of alcohol compounds, and (3) citric acid concentration of 20 mM -- far removed from the citric acid content suggested by Kagatani. This combination of citric acid concentration, specific concentration of specific alcohol, and surfactant is neither disclosed nor suggested by Kagatani. Accordingly, it is urged that the obviousness rejections over Kagatani should be withdrawn.

Obviousness Rejection over Grebow in view of Dua

Claims 15, 24-28, 30-33, 35-39 and 43-44 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Grebow (discussed above) in view of Dua et al. Among the limitation of claims 15, 24-28, 30, 33, 35-37, 39 and 43-44 that are neither disclosed nor suggested by the combination of references is the limitation that tonicity be 250-350 mOsm. The Examiner concedes that Grebow et al. does not disclose or suggest the specific tonicity claimed by applicant, but alleges that Dua teaches the use of any tonicity between 100 and 600 mOsm (Office Action, page 7, line 7). On the contrary, Dua specifically tests three subgroups of formulations within that range, and concludes that bioavailability is enhanced only in hypertonic or hypotonic solutions that are quite different from the isotonic 250-350 mOsm recited by Applicant.

Specifically, the table at the bottom of page 237 of the Dua reference tests isotonic, hypertonic, and hypotonic formulations at both low and high viscosity. Only the isotonic formulation (300 mOsm) is within the range recited by Applicant's claim 15. The hypertonic formulation was at 600 mOsm and the hypotonic formulation was at 100 mOsm. As reported in the Table at the bottom of page 237 of the Dua reference, the hypertonic (600 mOsm) and hypotonic (100 mOsm) formulations were taught by Dua to provide better bioavailability than the isotonic formulations at both high and low viscosity. At page 238, column 2, final sentence, Dua et al. conclude that "the bioavailability of the drug was enhanced in both the hypotonic and hypertonic

condition by 4-5 fold." Dua thus suggests that Applicant's recited 250-350 mOsm is to be avoided where, as here, bioavailability is an object. This teaching away by the prior art reference cannot suggest to one of skill in the art that applicants' claimed range be utilized. .

In addition to the foregoing deficiencies of the Dua reference, the citrate range set forth in the claims is also not suggested by either Grebow or Dua. Dua is silent on the subject, and Grebow is distinguishable for the reasons set forth above in connection with the obviousness rejection over Grebow. Claims 32 and 38 are dependent from claim 13 (directly or indirectly) and distinguish Grebow for the same reasons as does claim 13 (discussed above in connection with the prior rejection over Grebow alone). Dua's discussion of tonicity and viscosity does nothing to overcome the shortcomings of Grebow relative to claim 13, and by implication, claims 32 and 38 which are dependent therefrom.

For all of the foregoing reasons, it is urged that the rejection under 35 U.S.C. §103 Grebow in view of Dua be withdrawn.

Obviousness Rejection over Kagatani in view of Dua

Claims 14-15, 24-33, 35-39 and 43-44 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Kagatani in view of Dua.

The combination of these two references, however, fails to set forth a *prima facie* case of obviousness. As noted *supra* in connection with the prior obviousness rejection over Kagatani, Kagatani teaches a citrate concentration significantly above that recited by applicant in each of the rejected claims, and significantly above the level at which deterioration of shelf stability occurs. This concentration-dependent negative effect on shelf stability at higher concentrations is reported in Table 3 of Applicant's patent, and was not known or appreciated by Kagatani. The Dua reference adds nothing to this deficiency of Kagatani because it does not address citrate concentration at all, and instead addresses only tonicity.

Additionally, claims 15, 24-31, 33, 35-37, 39 and 43-44 further recite a tonicity (250-350 mOsm) that is neither disclosed nor suggested by either Kagatani or Dua. The Examiner notes at page 8 of the Office Action that Kagatani "lacks disclosure on specific tonicity . . . ." As noted above in connection with the prior obviousness rejection over the combination of Dua and Grebow, Dua teaches away -- not toward -- the 250-350 mOsm recited in the foregoing claims that address

tonicity. Thus, even if Dua and Kagatani were combined as suggested by the Examiner, applicant's nasal formulation would not result. The combination of Dua and Kagatani would instead result in citrate levels that are too high (as taught by Kagatani) and tonicity that is either too high or too low (as taught by Dua's findings that hypertonic or hypotonic formulations outperform isotonic formulations (e.g., the isotonic 250-350 mOsm range recited by Applicant in the above-noted claims). Accordingly, it is believed that the obviousness rejection over Kagatani in view of Dua should be withdrawn.

Anticipation Rejection over Grebow

Claims 22 and 23 stand rejected by the Examiner under 35 U.S.C. § 102 as allegedly anticipated by Grebow et al. At page 9 of the Office Action, the Examiner argues that column 11, lines 35-47 of Grebow teach applicant's claimed citrate concentration for the purpose of providing stability. Initially, it is pointed out that even if this were the case (and as noted below, Applicant believes that it is not) this would be relevant only to claim 22 (method of improving stability) and not to claim 23 (method of improving bioavailability). The relevant language, at column 11, lines 45-47, states that "this concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle." That statement immediately follows Grebow's statement of preference for the higher 50 to 200 mM concentration range that teaches away from applicant's invention. To the extent that Grebow was observing shelf stability in such a high range, it suggests that the Grebow reference may even have been focusing on one of its other buffer systems -- and not citrate. Otherwise, Grebow should have been seeing the same significant stability loss that applicant discovered at high citrate concentration ranges.

The Examiner further argues at page 9 of the Office Action that prior art use of citrate, which as noted above has been primarily for the purpose of buffering pH, would inherently result in improved stability and bioavailability in accordance with the claimed invention, thus creating inherency-type anticipation. However, anticipation under the doctrine of inherency would result only if the prior art's use of citrate as a buffer would always result in using citrate within applicant's critical range to provide the bioavailability and stability benefits that Applicant shows to result from that range. As the court stated in *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362,

1365 (Fed. Cir. 1999), "[o]ccasional results are not inherent." However, when citrate is used as Grebow used it, to effect pH, the concentration of citrate is highly variable depending (1) on the pH level targeted and (2) on the pH of the other components of the calcitonin formulation in the absence of citrate. It is noted that Grebow teaches an enormously broad target pH range - - anywhere from 3 to 8. (See Grebow, Col 11, lines 38-39). The amount of citrate buffer Grebow would use would also vary enormously depending on whether Grebow targets the lower end or higher end of this pH range, and further depending on the pH effects of other components of the Grebow formulations. In the 14 Grebow examples, citrate is frequently not used at all. When used, it is at highly varied concentrations. Only in the rarest of cases (as illustrated by Grebow's examples 7 and 10) would Grebow utilize citrate within Applicant's claimed range, and even then is ignoring Grebow's specifically stated preference for using a much higher concentration between 50 and 200 mM (See column 11, lines 44-45). Method claims such as claims 22 and 23 are not anticipated under the doctrine of inherency by the prior art stumbling onto the claimed range by accident on rare occasions, when the prior art's more typical situation is to the contrary. See *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result . . . is not sufficient."). Accordingly, it is urged that the rejection of claims 22 and 23 under 35 U.S.C. §102 should be withdrawn.

It is believed that the application is now in condition for allowance.

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop Reissue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 22, 2006:

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APPENDIX A

Claim Number (Status)	Nature of Change/Recitation	Supporting Text in Original Patent
1-12 (canceled)	n/a	n/a
13 (pending)	citric acid concentration; rewritten in independent form; "and/or" changed to Markush format	Table 1; Table 3
14 (pending)	claim dependency only	original claim 14
15 (pending)	citric acid concentration; rewritten in independent format; "and/or changed to Markush format	original claim 15; Table 1; Table 3
16 (pending)	claim dependency only	original claim 16
17 (pending)	claim dependency only	original claim 17
18 (pending)	no change	original claim 18
19 (pending)	typographical error "MRC"; no substantive change	original claim 19
20 (pending)	claim dependency only	original claim 20
21 (pending)	no change	original claim 21
22 (pending)	"about" removed	original claim 22
23 (pending)	"about" removed	original claim 23
24 (pending)	citric acid concentration	Table 1; Table 3
25 (pending)	pH range	col. 3, line 12
26 (pending)	pH range	col. 3, line 12
27 (pending)	aqueous saline	col. 3, line 2
28 (pending)	viscosity	col. 3, lines 19-20
29 (pending)	polyoxyethylene (20) sorbitan monooleate	original claim 16
30 (pending)	preservatives	original claim 17

Claim Number (Status)	Nature of Change/Recitation	Supporting Text in Original Patent
31 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18
32 (pending)	salmon calcitonin	examples 1, 2 and 3
33 (pending)	salmon calcitonin	examples 1, 2 and 3
34 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
35 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
36 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
37 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
38 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
39 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
40 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
41 (pending)	pH range; citric acid concentration	col. 3, line 12; Tables 1 and 3
42 (pending)	pH range; citric acid concentration	col. 3, line 12; Tables 1 and 3
43 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18
44 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18